Phase II Trial of *Nab*-Paclitaxel Compared With Docetaxel as First-Line Chemotherapy in Patients With Metastatic Breast Cancer: Final Analysis of Overall Survival

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Abstract

Strategies for optimizing taxane treatment have focused on modification of dosing schedules. This randomized phase II study compared the efficacy and safety of weekly and every 3 weeks (q3w) *nab*-paclitaxel versus docetaxel q3w as first-line treatment for metastatic breast cancer (MBC). Weekly *nab*-paclitaxel at 150 mg/m^2 demonstrated the best risk-to-benefit ratio and longest overall survival in this study.

Background: A randomized phase II study in first-line MBC demonstrated superior efficacy and safety of weekly *nab*-paclitaxel compared with docetaxel. Final survival analyses and updated safety results are reported. **Patients and Methods:** Three hundred two patients with no previous chemotherapy for MBC were randomized to receive *nab*-paclitaxel 300 mg/m^2 q3w, *nab*-paclitaxel 100 mg/m^2 or 150 mg/m^2 the first 3 of 4 weeks (qw 3/4), or docetaxel 100 mg/m^2 q3w. The trial was powered for analyses of antitumor activity and safety. **Results:** Treatment with *nab*-paclitaxel 150 mg/m^2 qw 3/4 resulted in a median overall survival (OS) of 33.8 months compared with 22.2, 27.7, and 26.6 months for *nab*-paclitaxel 100 mg/m^2 qw 3/4, *nab*-paclitaxel 300 mg/m^2 q3w, and docetaxel, respectively (overall $P = .047$). Patients receiving 150 mg/m^2 *nab*-paclitaxel had prolonged median OS compared with those in the 100 mg/m^2 *nab*-paclitaxel arm (hazard ratio, 0.575; $P = .008$). A trend toward a longer OS was noted in the 150 mg/m^2 *nab*-paclitaxel arm versus docetaxel arm (hazard ratio, 0.688). Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all *nab*-paclitaxel arms compared with docetaxel. **Conclusions:** Consistent with previously published efficacy results, these data suggest that 150 mg/m^2 qw 3/4 may represent the most clinically efficacious *nab*-paclitaxel dosing regimen for patients with no previous chemotherapy for MBC. A phase III trial confirming these results would be necessary and prudent before widespread adoption of the 150 mg/m^2 dose in clinical practice.

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Introduction

According to the recent SEER (Surveillance Epidemiology and End Results 1975-2008) cancer statistics, approximately 4 out of 5 women with metastatic breast cancer (MBC) will die within 5 years of diagnosis.[1] The primary goals of chemotherapeutic treatment of MBC are to prolong survival and to improve quality of life.[2,3] Taxanes, a class of potent anticancer drugs, play an important role in the treatment of MBC.[2,4,5] In clinical trials, single-agent docetaxel given at 100 mg/m^2 every 3 weeks (q3w) or solvent-based (sb) paclitaxel given at 90 mg/m^2 weekly led to a median overall survival (OS) of 31.9 and 25.2 months, respectively, in patients with MBC.[6,7] However, administration of both docetaxel and sb-paclitaxel are associated with a wide array of adverse events (AEs), including hypersensitivity reactions, neutropenia, and sensory neuropathy.[8-12] Additionally, the active agents of these drugs may be trapped in solvent micelles, limiting their availability to tumors and prolonging their systemic exposure, which in turn increases drug toxicity.[13] A novel albumin-bound 130-nm formulation of paclitaxel (*nab*-paclitaxel, Abraxane; Celgene Corporation, Summit, NJ) has been shown to improve the efficacy of taxane treatment, while limiting the toxicity typically associated with sb-paclitaxel and docetaxel.[14,15]

In a phase I trial involving patients with solid tumors, the maximum tolerated dose of *nab*-paclitaxel was 300 mg/m^2 q3w, which is considerably higher than the US Food and Drug Administration (FDA)-recommended dose of sb-paclitaxel.[11,16] The FDA-recommended dose of *nab*-paclitaxel for MBC is 49% higher than that of paclitaxel (260 mg/m^2 q3w vs. 175 mg/m^2 q3w).[11,17] The ability to deliver a higher dose of paclitaxel may, in part, reflect the advantage of using albumin to enhance the bioavailability of paclitaxel. The FDA-recommended dose of docetaxel, a closely related agent, is 60 to 100 mg/m^2 q3w for single-agent treatment of MBC.[12]

Recent efforts to optimize taxane treatment have focused on modifying the dosing schedules used for the respective agents. Rivera et al demonstrated that docetaxel given at 75 mg/m^2 q3w produced greater clinical efficacy than docetaxel given at 35 mg/m^2 on a weekly schedule,[18] whereas sb-paclitaxel appeared to be more effective when administered on a weekly schedule.[19] The efficacy and safety of *nab*-paclitaxel administered as a weekly schedule has been investigated in patients with advanced malignancies.[20] In a phase I trial the maximum tolerated dose of *nab*-paclitaxel given on a first 3 of 4 weeks (qw 3/4) schedule was 150 mg/m^2.[20]

The current phase II study was conducted to evaluate the safety and efficacy of 3 *nab*-paclitaxel dosing regimens (300 mg/m^2 q3w, 150 mg/m^2 qw 3/4, and 100 mg/m^2 qw 3/4) and to investigate differences in safety and efficacy between these dosing regimens of *nab*-paclitaxel and docetaxel 100 mg/m^2 q3w for the first-line treatment of MBC. The primary end point of the study was overall response rate (ORR) by investigator assessment. Initial findings of this study demonstrated superior efficacy and safety of weekly *nab*-paclitaxel compared with docetaxel, with a statistically and clinically significant prolongation (>6 months) of progression-free survival (PFS) in patients receiving *nab*-paclitaxel 150 mg/m^2 qw 3/4 compared with docetaxel 100 mg/m^2 q3w.[14] By investigator assessment, the 150 mg/m^2 qw 3/4 *nab*-paclitaxel arm resulted in the highest ORR of 74% compared with 63% in the 100 mg/m^2 qw 3/4 arm (P = statistically nonsignificant [NS]), 46% in the 300 mg/m^2 q3w arm ($P = .002$), and 39% in the docetaxel arm ($P < .001$).[14] Investigator-assessed median PFS was longest in the *nab*-paclitaxel arm at 150 mg/m^2 qw 3/4 (14.6 months) compared with *nab*-paclitaxel 100 mg/m^2 qw 3/4 (7.5 months; $P = .001$), *nab*-paclitaxel 300 mg/m^2 q3w (10.9 months; P = NS), and docetaxel (7.8 months; $P = .012$) arms.[14] These results were supported by independent radiologist assessment. At the time of the publication of the initial analysis of the ORR (the primary study end point), the OS data were not yet mature. This report describes the final analysis of OS and updated safety outcomes.

Patients and Methods

The patients and methods for this trial were previously described.[14] Patients aged 18 years or older with stage IV pathologically confirmed adenocarcinoma of the breast, measurable disease, Eastern Cooperative Oncology Group performance status of 0 to 2, and no previous chemotherapy for MBC were eligible for inclusion. If sensory neuropathy was present, it must have been less than or equal to grade 1. Prior neoadjuvant or adjuvant chemotherapy was allowed. However, if adjuvant therapy included a taxane, it was required that at least 1 year had elapsed since therapy. Patients were excluded if they were receiving concurrent immunotherapy or hormonal therapy for breast cancer, had parenchymal brain metastases (unless stable), had a history of class II to IV congestive heart failure, or had any other malignancy within the last 5 years that could affect the diagnosis or assessment of breast cancer.

Study Design

This was an open-label, randomized, phase II study conducted at multiple sites in Russia and the United States. This study was performed in compliance with Good Clinical Practice, Guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Written informed consent was obtained from each patient before enrollment.

Patients were randomly assigned via a centralized randomization system (no stratification) to receive 1 of the following 4 treatment regimens (1:1:1:1 ratio): *nab*-paclitaxel over 30 minutes (300 mg/m^2 administered on day 1 of each 3-week cycle); 100 mg/m^2 administered weekly on days 1, 8, and 15 of each 4-week cycle; or 150 mg/m^2 administered weekly on days 1, 8, and 15 of each 4-week cycle; or docetaxel 100 mg/m^2 administered on day 1 of each 3-week cycle by intravenous infusion over 1 hour. The dose of *nab*-paclitaxel could be reduced by 20%, and patients in the docetaxel arm were permitted a dose reduction of 25%. Patients receiving docetaxel were given oral corticosteroids starting 1 day before administration for 3 days. No premedication to prevent hypersensitivity reactions was required before administration of *nab*-paclitaxel.

Study End Points

The primary efficacy end point was investigator-assessed ORR, which was defined as the percentage of patients who achieved an objective confirmed overall complete response or partial response based on Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[21] Secondary efficacy end points included disease control rate, PFS, duration of response, and OS. The data for OS and time to disease progression were collected monthly beginning 1 month after the end of study for 6 months, and then every 3 months for a total of

Table 1 Baseline Patient Characteristics

	nab-Paclitaxel			Docetaxel
	Arm A; 300 mg/m^2 q3w (n = 76)	Arm B; 100 mg/m^2 qw 3/4 (n = 76)	Arm C; 150 mg/m^2 qw 3/4 (n = 74)	Arm D; 100 mg/m^2 q3w (n = 74)
Age in Years, Mean	51.7	55.4	53.3	55.4
≥65, n (%)	9 (12)	14 (18)	10 (14)	19 (26)
Race, n (%)				
White	74 (97)	75 (99)	74 (100)	74 (100)
Hispanic or Latino	2 (3)	1 (1)	0	0
Body Weight in kg, Mean	72.6	73.6	76.2	76.0
Postmenopausal, n (%)	49 (64)	62 (82)	53 (72)	60 (81)
ECOG Performance Status, n (%)				
≤1	69 (91)	72 (95)	69 (93)	72 (97)
2	7 (9)	4 (5)	5 (7)	2 (3)
Previous Grade 1 Sensory Neuropathy, n (%)	9 (12)	6 (8)	9 (12)	7 (9)
Site of Metastases, n (%)				
Visceral[a]	64 (84)	61 (80)	59 (80)	67 (91)
Nonvisceral	12 (16)	15 (20)	15 (20)	7 (9)
Previous Chemotherapy, n (%)				
Adjuvant	27 (36)	20 (26)	24 (32)	29 (39)
Neoadjuvant	14 (18)	14 (18)	11 (15)	14 (19)
Metastatic	1 (1)	0	0	0
Time in Months From Initial Diagnosis to Metastatic Disease, Median (Range)[b]	13.7 (0-115.2)	12.9 (0-172.6)	10.5 (0-203.2)	14.5 (0-160.8)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; q3w = every 3 weeks; qw 3/4 = first 3 of 4 weeks.
[a] Visceral disease included patients with lung, liver, brain, pelvic, or peritoneal metastases.
[b] Overall, 32% of patients had a primary diagnosis of metastatic disease.

24 months. The safety/tolerability end points were the incidence of treatment-emergent and treatment-related AEs and serious AEs.

Assessments

Antitumor activity was evaluated every 8 weeks by investigators, using the RECIST criteria in patients with measurable disease (regardless of treatment regimen), as described previously.[14] Patients continued receiving treatment unless they developed progressive disease or unacceptable toxicity. After completion of enrollment, the protocol was amended to include an independent blinded radiologic assessment of response. For safety/tolerability evaluation, investigator-assessed incidences of treatment-related AEs were reported. Laboratory abnormalities, nadir of myelosuppression, and incidence of dose modifications, dose interruptions, and/or premature discontinuation of study drug were also recorded. All toxicities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events.

Statistical Methods

Planned enrollment was 300 patients (75 patients per arm). This sample size was selected to permit comparisons of toxicity between the regimens and to provide preliminary data with respect to antitumor activity of each arm. The approximate power to detect a 0.5-grade change of maximum degree of myelosuppression was 80%, and the power to detect a 0.4-grade change of sensory neuropathy was 84% (type I error = 0.05).

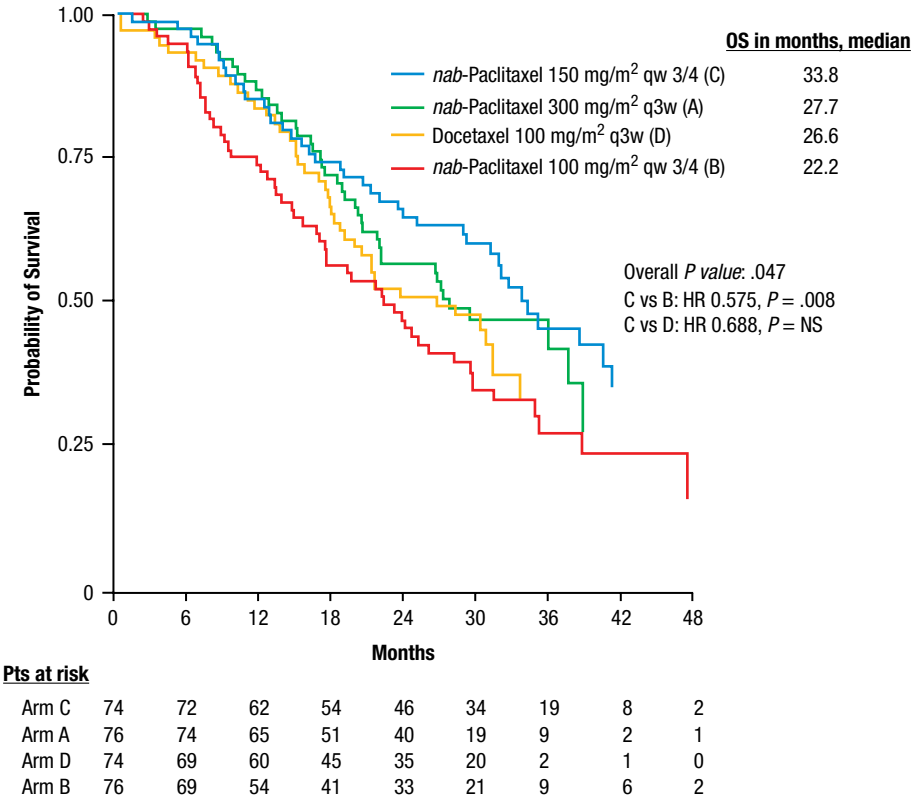
Safety and efficacy analyses were performed on the treated population (ie, all randomly assigned patients who received at least 1 dose of study drug). OS was analyzed using the Kaplan–Meier method, and *P* values were based on the log-rank test. Patients were censored at last known time they were alive. Death or censoring occurred at any time through follow-up. To avoid a multiple comparison adjustment for pairwise comparisons of the 4 treatment groups, a step-down approach was used to compare treatment groups. A 3-*df* overall test was performed first and pairwise comparisons were subsequently performed only if the overall test demonstrated a significant difference. The first pairwise comparison was made between the pair of treatment groups that had the largest difference. The same rule was applied to the next step and continued until no significant difference was observed or all pairwise comparisons were performed.

Results

Patients

Between November 2005 and June 2006, 302 patients enrolled in this trial. Two patients did not receive study drug and were not evaluable for response. Baseline patient characteristics were balanced

Figure 1 Overall Survival by Study Arm



Kaplan–Meier estimates for overall survival (as assessed by local investigators for each treatment arm).
Abbreviations: HR = hazard ratio; OS = overall survival; Pts = patients; q3w = every 3 weeks; qw 3/4 = first 3 of 4 weeks.

among the 4 treatment groups (Table 1). Patients in the 150 mg/m^2 *nab*-paclitaxel arm exhibited the shortest duration between initial diagnosis of breast cancer and diagnosis of metastatic disease (10.5 months vs. 12.9-14.5 months), although these differences were not statistically significant (Table 1).

Overall Survival

Median OS was 33.8 (95% confidence interval, 29.1-41.3) months with *nab*-paclitaxel given 150 mg/m^2 qw 3/4 compared with 22.2, 27.7, and 26.6 months in patients receiving *nab*-paclitaxel 100 mg/m^2 qw 3/4, *nab*-paclitaxel 300 mg/m^2 q3w, and docetaxel, respectively (overall P = .047) (Figure 1). Patients in the 150 mg/m^2 qw 3/4 *nab*-paclitaxel arm had a significantly prolonged median OS compared with those in the 100 mg/m^2 qw 3/4 *nab*-paclitaxel arm (33.8 vs. 22.2 months; P = .008; hazard ratio [HR] = 0.575). A trend toward prolonged median OS was observed among patients who received 150 mg/m^2 qw 3/4 *nab*-paclitaxel compared with those in the docetaxel q3w arm (26.6 months; HR = 0.688). Consistent with the OS results, more patients were alive and progression-free at the completion of the protocol-specified 2-year survival follow-up period in the 150 mg/m^2 qw 3/4 *nab*-paclitaxel arm (42%) compared with the 100 mg/m^2 qw 3/4 *nab*-paclitaxel arm (22%) and docetaxel arm (35%) (Table 2).

No statistical difference was noted in the median OS among the treatment groups for different patient subsets, including age younger than 65 years versus 65 years or older, visceral versus nonvisceral, number of visceral lesions less than 5 versus 5 or more, and premenopausal versus postmenopausal (Table 3). Median OS trended in favor of the 150 mg/m^2 qw 3/4 arm in each patient subset: age younger than 65 years versus 65 years or older, visceral disease versus nonvisceral disease, and number of visceral lesions less than 5 versus 5 or more.

Treatment Exposure

The median dose intensity for the 150 mg/m^2 *nab*-paclitaxel arm was higher than in the 100 mg/m^2 *nab*-paclitaxel group (101 mg/m^2 per week vs. 75 mg/m^2 per week) and similar to the q3w 300 mg/m^2 *nab*-paclitaxel dose (100 mg/m^2 per week) (Table 4). More dose reductions occurred in patients in the 150 mg/m^2 qw 3/4 *nab*-paclitaxel arm (47%) compared with the other treatment arms (18% and 20% in the 100 mg/m^2 qw 3/4 and 300 mg/m^2 q3w *nab*-paclitaxel arms, respectively, and 30% in the docetaxel arm) (Table 4). More

Table 2 Overall Survival Analysis

	nab-Paclitaxel			Docetaxel
	Arm A; 300 mg/m^2 q3w (n = 76)	Arm B; 100 mg/m^2 qw 3/4 (n = 76)	Arm C; 150 mg/m^2 qw 3/4 (n = 74)	Arm D; 100 mg/m^2 q3w (n = 74)
Deaths, n (%)	41 (54)	53 (70)	39 (53)	42 (57)
Patients Censored, n (%)	35 (46)	23 (30)	35 (46)	32 (43)
Reasons for Censoring, n (%)				
Ongoing Study Treatment	0	0	1 (1)	0
Ongoing Survival Follow-Up Period	1 (1)	2 (3)	0	0
Completed 2-Year Follow-Up Period	30 (39)	17 (22)	31 (42)	26 (35)
Lost to Follow-Up	4 (5)	4 (5)	3 (4)	6 (8)

Abbreviations: q3w = every 3 weeks; qw 3/4 = first 3 of 4 weeks.

Table 3 Overall Survival by Patient Subsets

OS in Months[a]	*nab*-Paclitaxel						Docetaxel		Overall *P* Value[b]
	Arm A; 300 mg/m^2 q3w		Arm B; 100 mg/m^2 qw 3/4		Arm C; 150 mg/m^2 qw 3/4		Arm D; 100 mg/m^2 q3w		
	n	Median	n	Median	n	Median	n	Median	
All Patients	76	27.7	76	22.2	74	33.8	74	26.6	.047
<65 years	67	27.7	62	23.0	64	32.8	55	21.4	.171
≥65 years	9	>30.5	14	17.3	10	>45.9	19	31.3	.170
DM									
Visceral	64	27.1	61	19.6	59	32.1	67	21.4	.093
Nonvisceral	12	36.0	15	29.7	15	>48.4	7	>35.4	.405
Lesion Sites									
<5	39	29.5	37	23.0	38	34.3	41	30.2	.240
≥5	25	21.7	24	14.7	21	29.1	26	18.0	.290
Premenopausal	26	26.7	14	15.6	21	32.1	12	>35.4	.399
Postmenopausal	49	36.0	62	23.7	53	38.7	60	28.2	.134

Abbreviations: DM = dominant metastasis; OS = overall survival; q3w = every 3 weeks; qw 3/4 = first 3 of 4 weeks.
[a] OS by investigator assessment.
[b] By log-rank test.

patients in the 150 mg/m^2 *nab*-paclitaxel arm required dose delays (81%) compared with patients in the other treatment arms (43% and 45% in the 300 mg/m^2 q3w and 100 mg/m^2 qw 3/4 *nab*-paclitaxel arms, respectively, and 34% in the docetaxel arm).

Although dose reductions and dose delays occurred more frequently in the 150 mg/m^2 *nab*-paclitaxel arm compared with the other treatment groups, the median duration of treatment was longest in that arm (38 vs. 22 weeks in the 300-mg/m^2 *nab*-paclitaxel arm [$P = .001$], 30 weeks in the 100 mg/m^2 *nab*-paclitaxel arm [$P =$ NS], and 21 weeks in the docetaxel arm [$P < .001$]) (Table 4). Furthermore, for the *nab*-paclitaxel arms, dose reductions occurred at a median cycle of 4, 5, and 7 for the 150, 100, and 300 mg/m^2 arms, respectively. Patients receiving docetaxel required dose reductions at cycle 3. Best response occurred at cycle 2 for patients receiving 150 mg/m^2 qw 3/4 or 100 mg/m^2 qw 3/4 *nab*-paclitaxel, whereas the median cycle at best response occurred at cycle 4 and cycle 5 for the 300 mg/m^2 q3w *nab*-paclitaxel arm and the docetaxel arm, respectively ($P < .001$ for each comparison) (Table 4).

Analysis of the effect of prior or secondary therapies on OS outcomes showed no difference in the rates of prior neoadjuvant or adjuvant chemotherapy (39%-46%) and secondary therapy (76%-82%) among the treatment arms (Table 5). The difference in the lengths of time from the end of prior chemotherapy to the diagnosis of metastatic disease between the treatment arms were not statistically significant, nor were the differences in the lengths of time to secondary treatment after discontinuation of study treatment.

Safety Update

Updated safety results for grade 3 to 4 neutropenia, sensory neuropathy, and fatigue are presented in Table 6. Grade 4 neutropenia (75% vs. 5%-9%), febrile neutropenia (8% vs. 1%), and grade 3 fatigue (19% vs. 0%-5%) occurred more frequently in the docetaxel

Table 4 Treatment Exposure

	nab-Paclitaxel			Docetaxel	Overall *P* Value	Pairwise *P* Value
	Arm A; 300 mg/m^2 q3w (n = 76)	Arm B; 100 mg/m^2 qw 3/4 (n = 76)	Arm C; 150 mg/m^2 qw 3/4 (n = 74)	Arm D; 100 mg/m^2 q3w (n = 74)		
Dose Intensity in mg/m^2 Per Week						
Median	100	75	101	33	NA	
Target	100	75	112.5	33		
Patients With 1 Dose Reduction, n (%)[a]	15 (20)	14 (18)	35 (47)	22 (30)	< .001[b]	A vs. C: < .001; B vs. C: < .001; C vs. D: <.042
Patients With ≥1 Dose Delay, n (%)	33 (43)	34 (45)	60 (81)	25 (34)	< .001[b]	A vs. C: < .001; B vs. C: < .001; C vs. D: < .001
Duration of Treatment in Weeks, Median (Range)	22 (<1 to 125)	30 (2-123)	38 (2-107)	21 (<1 to 109)	< .001[c]	A vs. C: .001; B vs. D: < .001; C vs. D: < .001
Cycle of Dose Reduction, Median (Range)	7 (2-13)	5 (2-13)	4 (1-19)	3 (2-13)	.101[c]	
Cycle at Best Response, Median (Range)	4 (3-21)	2 (2-8)	2 (2-15)	5 (2-18)	< .001[c,d]	A vs. B: < .001; A vs. C: < .001; B vs. C: < .001; C vs. D: < .001
Cycles Administered, Median (Range)	8 (1-39)	8 (1-30)	10 (1-27)	8 (1-37)	.160[c]	

Abbreviations: q3w = every 3 weeks; qw 3/4 = first 3 of 4 weeks.
[a] One dose reduction per patient was allowed.
[b] Based on Fisher Exact test.
[c] Based on Kruskal-Wallis test.
[d] Based on investigator assessment of patients who exhibited a confirmed response.

arm compared with the *nab*-paclitaxel arms. No cases of grade 4 sensory neuropathy were reported in any treatment arm. Grade 3 sensory neuropathy was most frequent in the 150 mg/m^2 qw 3/4 *nab*-paclitaxel arm. Neutropenia and sensory neuropathy were the most common toxicities leading to dose reduction in the *nab*-paclitaxel arms whereas neutropenia and febrile neutropenia were the most common toxicities leading to dose reduction in the docetaxel arm (Table 6). Median times to improvement of grade 3 sensory neuropathy to grade 2 or lower were 20 to 22 days for the *nab*-paclitaxel arms versus 41 days in the docetaxel arm (P = NS).

Discussion

Based on event-driven analysis of final OS in this randomized, phase II trial, the *nab*-paclitaxel 150 mg/m^2 qw 3/4 regimen provides the best clinical benefit-to-risk ratio for the first-line treatment of patients with MBC. The median OS of 33.8 months in this arm compares favorably with historical values for single-agent taxane therapy for MBC.[6,7,15]

The OS results presented here are consistent with the previous publication of ORR and PFS from this trial.[14] While similar to results seen in other studies of untreated MBC patients, the OS in the 100 mg/m^2 qw 3/4 arm was inferior to that seen in the 150 mg/m^2 qw 3/4 arm. By investigator assessment, treatment with *nab*-paclitaxel at 150 mg/m^2 qw 3/4 produced a statistically significant longer PFS than the q3w docetaxel arm: 14.6 versus 7.8 months (HR = 0.568; P = .012). In the current analysis, treatment with 150 mg/m^2 qw 3/4 *nab*-paclitaxel resulted in a 7.2-month prolongation of OS compared with docetaxel (HR = 0.688; P = NS).

At the time of the initial publication on the primary study end point only 133 deaths had occurred, representing 44% of the treated patient population. The current analysis is based on 175 deaths (maturity of 58%) in the treated patient population. Based on the constraints of the study design, patients who had completed the protocol-specified 2-year follow-up period were censored during the final OS analysis. As a result, approximately 40% of the treated patient population was censored for OS at the time of the final analysis. The majority of patients that were censored were alive at the end of the follow-up period. Of note, a relatively higher proportion of patients (46%) in the *nab*-paclitaxel at 150 mg/m^2 qw 3/4 compared with the other treatment arms (22%-39%) were censored after 2 years of follow-up. Classifying the study population into specific subsets based on age, location of dominant metastasis, number of metastatic lesions, or menopausal status revealed consistent trends in OS observed for the overall patient population.

Dose reductions and delays effectively managed the toxicities that occurred in the weekly 150 mg/m^2 *nab*-paclitaxel arm, enabling patients in that treatment arm to receive the longest duration of treatment in this trial (38 weeks vs. 21-30 weeks). As expected, taxane-associated neutropenia and peripheral neuropathy were the most common toxicities associated with dose reductions. The 150 mg/m^2 qw 3/4 *nab*-paclitaxel schedule was associated with a higher rate of dose reductions compared

Table 5 Prior and Secondary Therapies

	nab-Paclitaxel			Docetaxel	Overall *P* Value
	Arm A; 300 mg/m^2 q3w (n = 76)	Arm B; 100 mg/m^2 qw 3/4 (n = 76)	Arm C; 150 mg/m^2 qw 3/4 (n = 74)	Arm D; 100 mg/m^2 q3w (n = 74)	
Previous Therapy, n (%)					
Neoadjuvant	14 (18)	14 (18)	11 (15)	14 (19)	
Adjuvant	27 (36)	20 (26)	24 (32)	29 (39)	
Previous Chemotherapy, n (%)	35 (46)	30 (39)	29 (39)	34 (46)	.727[a]
Previous Hormone Therapy, n (%)	21 (28)	23 (30)	24 (32)	30 (41)	.380[a]
Time From End of Prior Chemotherapy to Metastatic Disease in Months, Median (Range)	20.3 (1.2-106.2)	15.0 (0.5-169.0)	26.6 (0.9-124.3)	21.9 (0.6-146.8)	.454[b]
Secondary Therapies, n (%)	60 (79)	58 (76)	57 (77)	61 (82)	.807[a]
Antineoplastic	41 (54)	39 (51)	29 (39)	36 (49)	.298[a]
Endocrine	18 (24)	19 (25)	26 (35)	28 (38)	.147[a]
Time to Secondary Treatment After Discontinuation of Study Treatment in Days, Mean	42	39	42	60	.439[c]

Abbreviations: q3w = every 3 weeks; qw 3/4 = first 3 of 4 weeks.
[a] Based on Fisher's exact test.
[b] Based on Kruskal–Wallis test.
[c] Based on analysis of variance test.

with the other treatment arms. Despite a higher frequency of dose reductions and delays, the median dose intensity achieved with 150 mg/m^2 *nab*-paclitaxel qw 3/4 (101 mg/m^2 per week) was greater than that achieved with 100 mg/m^2 *nab*-paclitaxel qw 3/4 (75 mg/m^2 per week) and similar to the 300 mg/m^2 *nab*-paclitaxel q3w dose (100 mg/m^2 per week). Moreover, the median cycle at dose reduction for the 150 mg/m^2 qw 3/4 *nab*-paclitaxel arm was cycle 4, whereas the median cycle of best response was observed in cycle 2. Thus, dosing at 150 mg/m^2 qw 3/4 appears to be effective, even in patients who require dose modification.

The rates of use of previous chemotherapy and secondary therapy were similar among the trial arms. Of note, approximately a third of patients in this study received secondary endocrine therapy. These data suggest that the types of prior and secondary therapy were unlikely to have had a significant impact on the differences observed in OS.

The safety profile of the qw 3/4 schedule of *nab*-paclitaxel is consistent with a previous report and no notable or unexpected toxicities were observed with prolonged treatment.[14] Of note, development of febrile neutropenia was rare among patients treated with *nab*-paclitaxel compared with those who received docetaxel. As may be expected, the longer median duration of treatment and dose intensity achieved in the 150 mg/m^2 qw 3/4 *nab*-paclitaxel arm was associated with an increased incidence of neuropathy. The incidence of grade 3 sensory neuropathy was similar between the 150 mg/m^2 qw 3/4 and 300 mg/m^2 q3w *nab*-paclitaxel arms and higher than in the 100 mg/m^2 qw 3/4 *nab*-paclitaxel and docetaxel arms; however, no grade 4 events were observed. The median time to improvement of sensory neuropathy to grade 2 or lower was considerably shorter for *nab*-paclitaxel (20-22 days) than with docetaxel (41 days). This time to improvement in patients receiving *nab*-paclitaxel was similar to previously published data (median 22 days).[15] Interestingly, grade 3 sensory neuropathy occurred at a substantially higher rate in the 300 mg/m^2 q3w *nab*-paclitaxel arm in this trial than in the 260 mg/m^2 arm in a previous phase III trial of *nab*-paclitaxel in patients with MBC (21% vs. 10%).[15]

In order to verify the OS data (a secondary end point) from the randomized phase II trial presented here, a subsequent trial would need to address some of the limitations of the current trial. While the OS value for *nab*-paclitaxel at 150 mg/m^2 qw 3/4 is promising, this trial was designed to detect statistical differences in ORR and safety, not OS. Furthermore, the current trial did not call for the collection of the important baseline characteristics of the status of estrogen and progesterone receptors and human epidermal growth factor receptor 2. These data would aid in determining the extent to which differences in OS could be attributed to differences in the patient populations of the individual treatment arms. These trial design modifications in the context of a large, randomized phase III trial would allow for a more robust comparison of OS in previously untreated MBC patients receiving *nab*-paclitaxel versus docetaxel.

Conclusion

nab-Paclitaxel at 150 mg/m^2 qw 3/4 resulted in a 33.8 month OS, a longer OS than historically achieved with single-agent taxane therapy in MBC. These findings are consistent with our previously published outcomes for investigator-assessed ORR and PFS.[14] No notable or unexpected toxicities were observed with treatment with *nab*-paclitaxel in this patient population. Although a higher rate of peripheral neuropathy was observed in the *nab*-paclitaxel 150 mg/m^2 qw 3/4 arm, the median time to improvement of sensory neuropathy to grade 2 or lower was considerably shorter for *nab*-paclitaxel compared with docetaxel and

Table 6 Safety Update

Adverse Event, n (%)	*nab*-Paclitaxel			Docetaxel	Overall *P* Value	Pairwise *P* Value
	Arm A; 300 mg/m^2 q3w (n = 76)	Arm B; 100 mg/m^2 qw 3/4 (n = 76)	Arm C; 150 mg/m^2 qw 3/4 (n = 74)	Arm D; 100 mg/m^2 q3w (n = 74)		
Neutropenia						
Grade 3	28 (37)	15 (20)	26 (35)	14 (19)	< .001[b]	A vs. B: .011; A vs. D: < .001; B vs. C: .016; B vs. D: < .001; C vs. D: < .001
Grade 4	5 (7)	4 (5)	7 (9)	54 (75)[a]		
Mean Nadir ± SD, × 10^9/L	1.21 ± 1.00	1.51 ± 0.96	1.11 ± 0.63	0.38 ± 0.34		
Sensory Neuropathy						
Grade 3	16 (21)	7 (9)	16 (22)	9 (12)	.083[b]	
Grade 4	0	0	0	0		
Fatigue						
Grade 3	4 (5)	0	3 (4)	14 (19)	< .001[b]	A vs. D: .012; B vs. D: < .001; C vs. D: .008
Grade 4	0	0	0	0		
Adverse Events Leading to Dose Reduction[c]						
Neutropenia	2 (3)	8 (11)	20 (27)	8 (11)		< .0001[b]
Febrile Neutropenia	0	1 (1)	1 (1)	6 (8)		.0086[b]
Sensory Neuropathy	9 (12)	4 (5)	11 (15)	1 (1)		.0074[b]
Fatigue	1 (1)	0	0	3 (4)		.1033[b]
Time to Onset of Sensory Neuropathy in Days, Median[d]	151	189	162	176	.454[e]	
Time to Improvement of Sensory Neuropathy in Days, Median[f]	22	22	20	41	.154[e]	

Abbreviations: q3w = every 3 weeks; qw 3/4 = first 3 of 4 weeks.
[a] The docetaxel arm produced higher rates of grade 4 neutropenia vs each *nab*-paclitaxel arm ($P < .001$ for each comparison).
[b] Based on Fisher Exact test.
[c] Adverse events leading to dose reduction in more than 1 patient reported.
[d] Grade 3 sensory neuropathy.
[e] Based on log-rank test.
[f] Improvement to grade 2 or lower.

similar among the 3 *nab*-paclitaxel arms. These data suggest that the 150 mg/m^2 qw 3/4 regimen of *nab*-paclitaxel may allow patients to achieve a clinical response before the emergence of dose-limiting AEs. A phase III trial confirming these results would be necessary and prudent before widespread adoption of the 150 mg/m^2 dose in clinical practice.

Clinical Practice Points

- Taxane-based chemotherapy is a standard management option for patients with MBC and results in prolonged progression-free and OS. Docetaxel at 75 mg/m^2 q3w is more effective than 35 mg/m^2 weekly dosing, whereas sb-paclitaxel (80 mg/m^2) is more effective when given weekly.
- Administration of sb-taxanes is associated with several AEs, including hypersensitivity reactions, neutropenia, and sensory neuropathy.
- *nab*-Paclitaxel has been shown to improve the efficacy of taxane treatment, while limiting the toxicity typically associated with sb-taxanes.
- Based on event-driven analysis of final OS, the *nab*-paclitaxel 150 mg/m^2 qw 3/4 regimen provided the best clinical benefit for the first-line treatment of patients with MBC. The median OS of 33.8 months observed with *nab*-paclitaxel 150 mg/m^2 qw 3/4 regimen compares favorably with historical values for taxane therapy alone for MBC and is consistent with trends seen in investigator-assessed ORR and PFS.
- *nab*-Paclitaxel was generally well tolerated, and the safety profile is consistent with previous reports.
- A phase III trial confirming these results would be necessary and prudent before widespread adoption of the 150 mg/m^2 qw 3/4 dose in clinical practice.

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